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Formulation and evaluation of Gastro-retentive mucoadhesive Cefpodoxime Proxetil tablets

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Abstract
The present study was aimed at development of mucoadhesive gastro retentive tablets of Cefpodoxime Proxetil for controlled release and to develop innovative and suitable dosage form by the use of various polymers. Cefpodoxime Proxetil is an oral third generation cephalosporin antibiotic and is active against most Gram positive and Gram negative bacteria but it undergoes rapid metabolism in intestinal mucosa due to change in pH environment and hence decreased oral bio-availability. Different tablet formulations were prepared using different mucoadhesive polymers like Carbopol 974P, Chitosan, HPMC K4M and Sodium alginate in various combination ratios by direct compression method. All the developed formulations were subjected to various evaluation parameters such as physicochemical properties. Optimized formulation was decided based on drug release studies and gastric residence time. Formulation containing Sodium alginate and chitosan in combination (F8) exhibited maximum in vitro residence time of 10 hrs and *in vitro* release was up to 91%. Optimized formulation was further subjected to *in vitro* permeation, SEM studies and stability studies. Scanning Electron Microscopy (SEM) revealed smooth surface characteristics with increasing pore diameter indicating the diffusion mechanism of release. Stability studies was carried out as per ICH

Keywords: Cefpodoxime Proxetil, Carbopol, Chitosan, HPMC, Sodium alginate.

1. Introduction
Oral route of drug administration is the most convenient and commonly used method of drug delivery. Despite of considerable advancements in the drug delivery, oral delivery of drugs is the most preferred route because of its ease of administration and low cost of therapy and high level of patient compliance. Oral controlled release drug delivery system have drawn considerable attention as these systems provide drug release at a predetermined, predictable and controlled rate [1].

Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of the GIT (gastro intestinal tract) or those are less soluble in or are degraded by alkaline pH or they encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their [2].

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels

Table 1: Gastro retentive drug delivery systems vs. Conventional drug delivery systems

S. No	Parameter	Conventional Drug Delivery Systems	Gastro retentive drug delivery systems
1.	Toxicity	High risk of toxicity	Low risk of toxicity
2.	Patient compliance	Less	Improves patient compliance
3.	Drug with narrow Absorption window in Small intestine	Not suitable	Suitable
4.	Drugs having rapid Absorption through GIT	Not much Advantageous	Very much Advantageous
5.	Drug which degrades in the colon	Not much Advantageous	Very much Advantageous
6.	Drugs which are poorly soluble at an alkaline pH	Not much Advantageous	Very much Advantageous

Potential candidates for gastroretentive drug delivery system

1. Drugs that are primarily absorbed in the stomach eg. Amoxicillin.
2. Drugs that are poorly soluble in alkaline pH eg. Furosemide, Diazepam.
3. Drugs that have narrow absorption window eg. Levodopa, Methotrexate.
4. Drugs that degrade in the colon eg. Ranitidine, Metformin HCL.
5. Drugs that disturb normal colonic microbes eg Antibiotics against Helicobacter pylori.
6. Drugs rapidly absorbed from the GI tract eg Tetracycline.
7. Drugs acting locally in the stomach [3, 4, 5].

2. Materials and Methods

Cefpodoxime Proxetil, Carbopol 974P, HPMC K4M, Chitosan, Sod. Alginate, Magnesium Stearate, Methanol, Barium Sulphate, Sodium Chloride, Potassium DihydroOrthro Phosphate.

Preformulation Studies

Organoleptic Evaluation

It is white to light brownish white powder, having faint odor and has bitter taste.

UV Scan copy

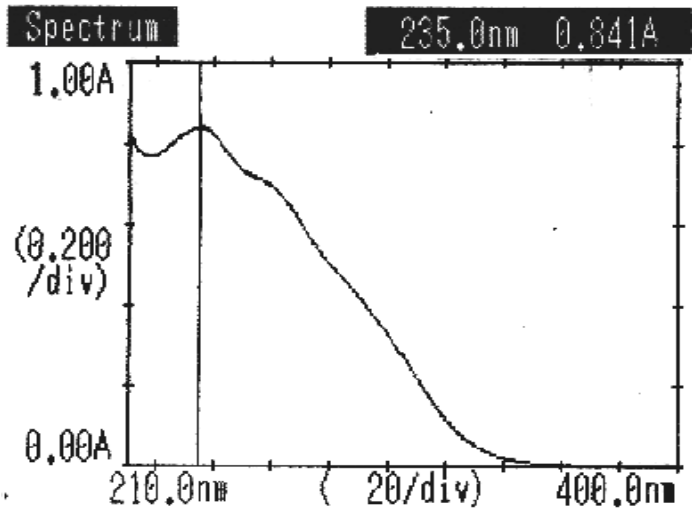
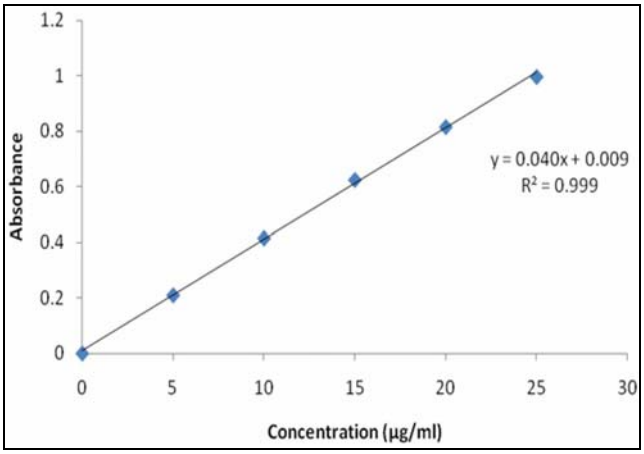


Fig 1: UV Absorption Spectrum of Cefpodoxime Proxetil

Standard calibration curve of Cefpodoxime Proxetil:



Infrared spectrum

FT-IR spectrum of Cefpodoxime proxetil (Fig 1). The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method (Schimadzu IR – Prestige-21 and observed for the charecterstic peaks of drug. FT- IR spectrum of drug shows major peaks at 3317.67, 2985.91, 1763.46, 1681.98, 1377.22, and 1053.17(cm -1) which corresponds to the –NH2, S-CH2, -C=O (lactam), -C=N-, -C-N- (aromatic primary amine) and C-Ostretching groups respectively, present in the Cefpodoxime proxetil molecule. (Fig 1).

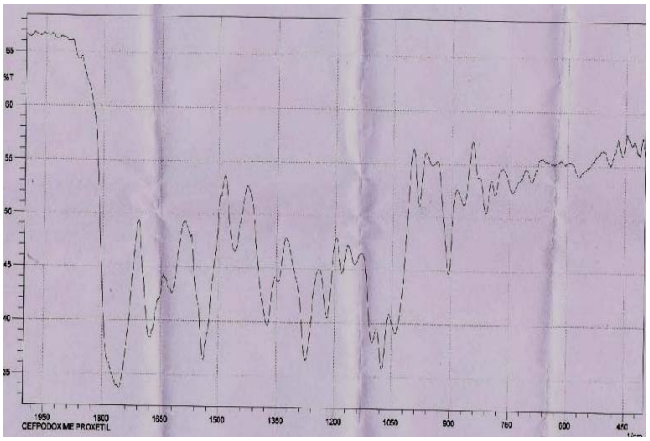


Fig. 2: IR Spectra of Pure Cepfodoxime Proxetil

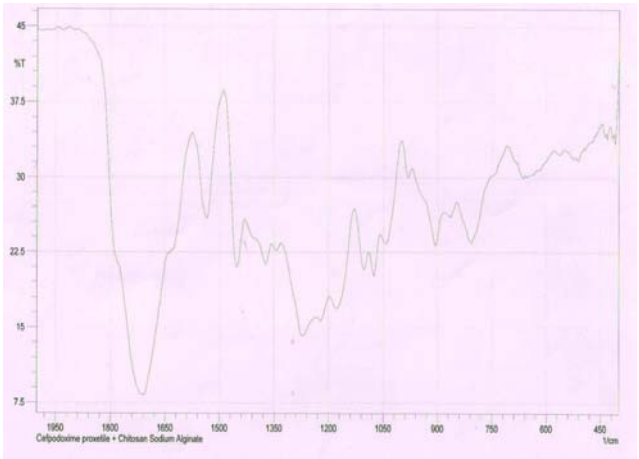


Fig 3: IR Spectra of Cepfodoxime Proxetil + Chitosan + Sod. Alginate

Table 2: Comparison of the peak of functional groups observed in IR spectra of compatibility studies

IR Spectra	Peak of functional groups [Wave length (cm^{-1})]			
	OH from H_2O and amide NH stretch	β- lactum C=O stretch	Amide C=O stretch	Carboxylate stretching O ⎮⎮ C = O
Sstandard Spectra	3500 – 3000 (broad band)	1760	1690	1600 (very broad)
Cefpodoxime Proxetil (CP)	3481.18-3357.62	1774.22	1678	1598.12
Cepfodoxime Proxetil + HPMC	3484.22	1774.63	1686.51	1610.11
Cefpodoxime Proxetil + Sod. Alginate	3524.81	1748.21	1703.83	1595.43
CP+Carbopol+HPMC	3477.40-3367.99	1786.43	1673.14	1591.60
CP+Chitosan	3480.40-3368.28	1782.36	1678.70	1596.15
CP+Sod. Alginate+Chitosan	3422.91 – 2925.82	1759.32	1687.63	1594.35
CP + Carbopol + Sod. Alginate	3438.62	1785.72	1688.44	1621.3
CP + Chitosan + Sod. Alginate	3521.21	1792.46	1702.27	1586.62
CP with Additives/Excepients	3368.80	1784.85	1673.78	1592.24

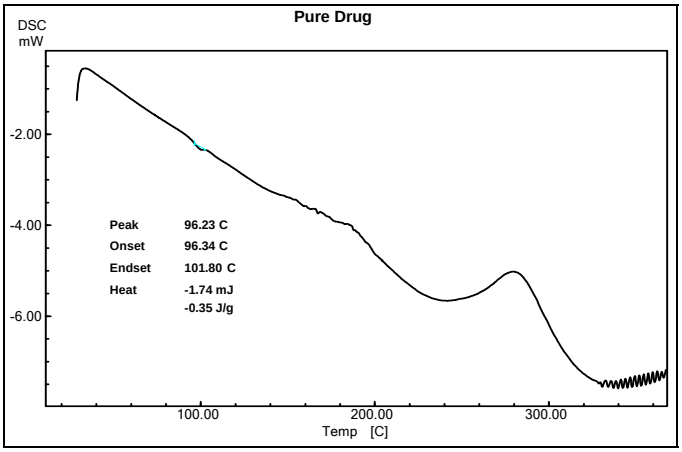


Fig 4: DSC of pure drug.

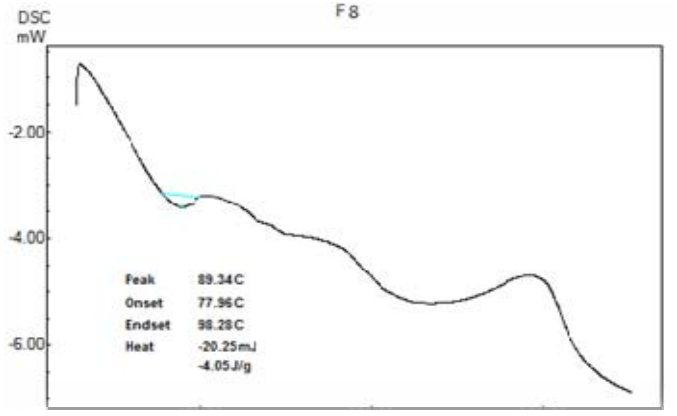


Fig 5: DSC of optimised formulation (Drug+Sodium alginate +Chitosan)

Table 3: Formulation design.

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Cefpodoxime Proxetil	200	200	200	200	200	200	200	200	200	200
2	HPMC K4M	105	105	105	105	-	-	-	-	70	70
3	Lactose	60	30	60	30	60	30	60	30	25	25
4	Carbopol 934P	70	100	-	-	70	100	-	-	70	-
5	Chitosan	-	-	-	-	105	105	105	105	70	70
6	Sod. Alginate	-	-	70	100	-	-	70	100	-	70
7	Mg. Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
8	Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total Table Not weight		450	450	450	450	450	450	450	450	450	450

Evaluation

Table 4: Evaluation parameters of formulations

Formulation code	Evaluation parameters				
	Thickness ± S.D. (mm) (n = 5)	Hardness ± S.D. (kg/cm^2) (n = 5)	Friability (%)	Average weight variation (%) (n=10)	Drug content (%)
F1	4.82 ± 0.043	6.75 ± 0.381	0.024	0.505 ± 0.011	88.83
F2	4.48 ± 0.055	6.28 ± 0.433	0.279	0.503 ± 0.010	90.37
F3	4.74 ± 0.085	6.42 ± 0.52	0.184	0.498 ± 0.010	92.01
F4	4.82 ± 0.067	6.75 ± 0.144	0.041	0.502 ± 0.135	94.83
F5	4.77 ± 0.054	6.33 ± 0.288	0.008	0.503 ± 0.009	92.62
F6	4.96 ± 0.048	6.49 ± 0.433	0.016	0.504 ± 0.010	94.02
F7	4.82 ± 0.028	6.41 ± 0.144	0.008	0.504 ± 0.008	96.80
F8	4.78 ± 0.039	6.59 ± 0.433	0.040	0.503 ± 0.008	95.53
F9	4.66 ± 0.026	6.72 ± 0.254	0.115	0.504 ± 0.008	96.25
F10	4.59 ± 0.016	6.82 ± 0.52	0.116	0.500 ± 0.009	97.46

Swelling index

Fig 6: Tablet after and before swelling.

Table 5: Swelling index values of the formulations

Formulations	Time in hours				
	2	4	6	8	24
F1	49.11	79.30	108.43	138.52	156.55
F2	46.71	58.48	116.31	166.78	175.82
F3	44.82	60.74	76.08	104.80	138.25
F4	11.11	73.61	121.80	184.72	195.83
F5	6.38	56.52	98.47	124.60	171.66
F6	4.86	139.86	191.66`	203.19	2O7.63
F7	16.87	48.89	130.66	185.76	Erosion
F8	6.66	60.00	133.33	181.52	Erosion
F9	23.33	46..55	89.34	128.88	164.32
F10	29.45	53.67	96.56	142.78	198.54

Table 6: Dissolution Profiles of all the Formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	14.5	17.7	16.32	13.66	14.4	16.1	13.24	15.27	18.3	20.2
2	19.8	26.7	26.64	22.3	25.43	21.8	22.11	26.64	35.1	32.2
3	24.6	34.6	34.01	28.68	33.21	34.4	31.9	38.62	50.3	43.21
4	31.2	43.7	37.44	39.69	42.85	40.7	36.9	47.7	54.4	50.44
5	30.4	50.1	43.14	46.2	50.21	52.8	41.2	55.49	59.5	62.12
6	46.2	64	46.58	53.68	58.4	62.3	47.7	64.8	65.5	70.43
7	56.2	61.4	52.7	62.28	62.12	73.3	51.7	71.36	71.34	77.22
8	71.4	74.3	65.72	70.21	70.6	80.7	73.7	78.44	76.54	80.62
9	82.3	82.4	83.7	78.3	75.43	86.9	88.4	86.42	86.8	85.31
10	91.6	89.8	91.5	86.42	84.31	94.67	94.82	92.89	89.88	92.32

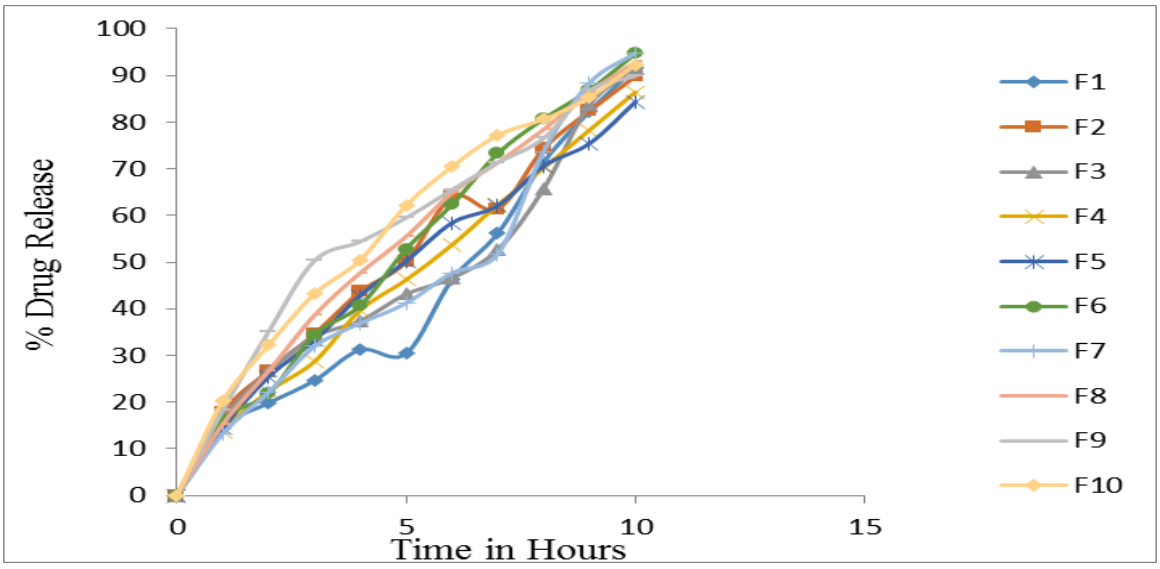


Fig 7: *In vitro* cumulative % drug released from all the formulations

Table 7: Curve Fitting Data of the release rate profile of Formulations. F1-F5.

Model		Formulation code				
		F_1	F_2	F_3	F_4	F_5
Krosmeyers – peppas	K	10.2661	11.3063	8.8340	11.0930	9.0286
	N	0.7386	0.6636	0.9088	0.7085	0.9202
	R	0.9967	0.9914	0.9990	0.9971	0.9996
Zero order	K	6.0796	5.8394	7.3045	6.1370	7.6975
	R	0.9740	0.9698	0.9946	0.9596	0.9985
First order	K	-0.081	-0.077	-0.1096	-0.0825	-0.1212
	R	0.9954	0.9900	0.9897	0.9926	0.9780
Higuchi matrix	K	16.085	15.464	19.1127	16.3208	20.0662
	R	0.9741	0.9744	0.9512	0.9847	0.9425
Best fit model		Peppas	Peppas	Peppas	Peppas	Peppas

Table 8: Curve Fitting Data of the release rate profile of Formulations. F6-F10.

Model		Formulation code				
		F_6	F_7	F_8	F_9	F10
Krosmeyers – peppas	6.5494	8.7249	9.1561	9.0504	11.6171	9.0286
	1.0638	0.8416	0.7481	0.8954	0.7734	0.9202
	0.9947	0.9982	0.9974	0.9922	0.9734	0.9996
Zero order	7.4655	6.3493	5.4789	7.3946	7.7317	7.6975
	0.9964	0.9921	0.9691	0.9884	0.9658	0.9985
First order	-0.1176	-0.0881	-0.0709	-0.1120	-0.1337	-0.1212
	0.9611	0.9952	0.9932	0.9839	0.8701	0.9780
Higuchi matrix	19.2752	16.6573	14.5272	19.3030	20.0899	20.0662
	0.9141	0.9576	0.9791	0.9374	0.8996	0.9425
Best fit model		Zero order	Peppas	Peppas	Peppas	Peppas

Table 9: Results of the stability studies

Time	Evaluation parameters			
	Colour	Hardness (kg/cm^2)	Drug content Uniformity (%)	% CDR
0 month	White	6.8	90.24	84.93
1 month	White	6.7	89.86	84.22
2 month	White	6.5	88.14	81.76
3 month	White	6.4	87.04	79.34

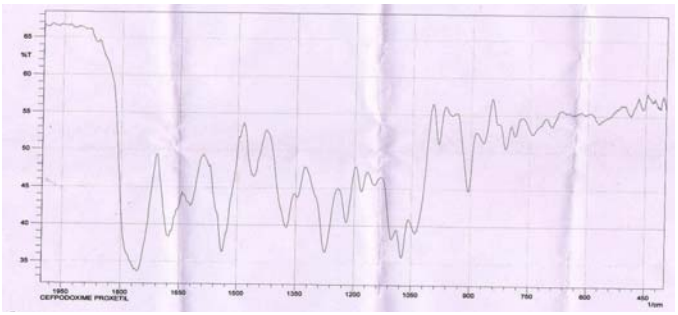


Fig 8: IR Spectra of Cefpodoxime Proxetil after three months

3. Conclusion and Discussion

The drugs which undergoes intestinal or enzymatic degradation in the stomach or Intestine can be successfully formulated into the Mucoadhesive drug delivery or gastroretentive drug delivery system can be used as an alternative method to conventional dosage form.

From the present research work the experimental results are concluded as follows:

The release of the drug Cefpodoxime Proxetil from mucoadhesive gastro retentive tablets is in a controlled and well regulated manner.

The formulation prepared in combination with Sodium Alginate and Chitosan showed maximum *in vitro* residence time, good in vitro drug release pattern.

The X –ray photographs pertaining to *in vivo* studies on Rabbits revealed that the tablet was in same position i.e. Muco-adhesive for up to 10 hours with change in physical properties (swelling).

The optimized formulation F8 found to be stable for period of 3 months and it is done stability studies according to ICH Guidelines.

So in final a promising controlled release muco-adhesive tablets of Cefpodoxime Proxetil have been developed successfully.

From the this research experimental data it can be concluded that a successful muco-adhesive control drug delivery system for Cefpodoxime Proxetil have been developed by using mucoadhesive polymers such as Sodium Alginate and Chitosan.

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